Clinical trial results:
Empagliflozin and its effect on heart failure in type 2 diabetes

Summary

EudraCT number	2016-000214-30
Trial protocol	DE
Global end of trial date	19 November 2020

Results information

Result version number	v1 (current)
This version publication date	25 January 2023
First version publication date	25 January 2023
Summary attachment (see zip file)	Adverse_events_EFFORT-2 (Adverse_events_EFFORT_2.pdf)

Trial information

Trial identification

Sponsor protocol code	P000805

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00009894

Notes:

Sponsors

Sponsor organisation name	Medical Center - University of Freiburg
Sponsor organisation address	Hugstetter Straße 55, Freiburg, Germany, 79106
Public contact	Coordinating Investigator, Medical Center - University of Freiburg, jochen.seufert@uniklinik-freiburg.de
Scientific contact	Coordinating Investigator, Medical Center - University of Freiburg, jochen.seufert@uniklinik-freiburg.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 November 2020
Global end of trial reached?	Yes
Global end of trial date	19 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the EFFORT study is to investigate effects of empagliflozin on quality of life in diabetic patients with HFrEF or HFpEF.

Protection of trial subjects:

Before enrolment in the clinical trial, the patient was informed that participation in the clinical trial is voluntary and that he/she may withdraw from the clinical trial at any time without having to give reasons and without penalty or loss of benefits to which the patient is otherwise entitled.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 63
Worldwide total number of subjects	63
EEA total number of subjects	63

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	26
From 65 to 84 years	37
85 years and over	0

Subject disposition

Recruitment	
Recruitment details: -	

Pre-assignment	
Screening details: -	

Pre-assignment period milestones	
Number of subjects started	63
Number of subjects completed	63

Period 1	
Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Empagliflozin
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Empagliflozin
Investigational medicinal product code	
Other name	Jardiance
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Dose: 25 mg/day. The tablets were to be taken in the morning, with or without food, swallowed whole with water.

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was supplied as optically identical tablets to the IMP containing lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate, hypromellose 2910, titanium dioxide, talc, macrogol 400, iron oxide, yellow.

Number of subjects in period 1	Empagliflozin	Placebo
Started	32	31
Completed	32	31

Baseline characteristics

Reporting groups	
Reporting group title	Empagliflozin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Empagliflozin	Placebo	Total
Number of subjects	32	31	63
Age categorical Units: Subjects			
Adults (18-64 years)	13	13	26
From 65-84 years	19	18	37
Gender categorical Units: Subjects			
Female	10	4	14
Male	22	27	49

Subject analysis sets	
Subject analysis set title	EFFORT-1
Subject analysis set type	Full analysis

Subject analysis set description:

The primary objective of the EFFORT-1 study is to investigate effects of empagliflozin on quality of life in diabetic patients with heart failure (HF) with reduced ejection fraction (HFrEF). EFFORT-1 was planned as a confirmative study with respect to the primary endpoint, and had to be changed to an exploratory study due to slow recruitment. The primary objective is to evaluate quality of life under treatment with empagliflozin as compared to placebo in diabetic patients with HFrEF.

Subject analysis set title	EFFORT-2
Subject analysis set type	Full analysis

Subject analysis set description:

The primary objective of the EFFORT-2 study is to investigate effects of empagliflozin on quality of life in diabetic patients with heart failure (HF) with preserved ejection fraction (HFpEF). EFFORT-2 is an exploratory hypotheses generating study. The primary objective is to evaluate quality of life under treatment with empagliflozin as compared to placebo in diabetic patients with HFpEF.

Reporting group values	EFFORT-1	EFFORT-2	
Number of subjects	24	39	
Age categorical Units: Subjects			
Adults (18-64 years)	13	13	
From 65-84 years	11	26	
Gender categorical Units: Subjects			
Female	2	12	
Male	22	27	

End points

End points reporting groups

Reporting group title	Empagliflozin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	EFFORT-1
Subject analysis set type	Full analysis

Subject analysis set description:

The primary objective of the EFFORT-1 study is to investigate effects of empagliflozin on quality of life in diabetic patients with heart failure (HF) with reduced ejection fraction (HFrEF). EFFORT-1 was planned as a confirmative study with respect to the primary endpoint, and had to be changed to an exploratory study due to slow recruitment. The primary objective is to evaluate quality of life under treatment with empagliflozin as compared to placebo in diabetic patients with HFrEF.

Subject analysis set title	EFFORT-2
Subject analysis set type	Full analysis

Subject analysis set description:

The primary objective of the EFFORT-2 study is to investigate effects of empagliflozin on quality of life in diabetic patients with heart failure (HF) with preserved ejection fraction (HFpEF). EFFORT-2 is an exploratory hypotheses generating study. The primary objective is to evaluate quality of life under treatment with empagliflozin as compared to placebo in diabetic patients with HFpEF.

Primary: EFFORT-1: Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score

End point title	EFFORT-1: Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score

End point description:

Difference of Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score to baseline at 6 months after randomization. A lower MLHFQ score indicates less effect of heart failure on a patient's quality of life. A total score accounts for all 21 items.

End point type	Primary

End point timeframe:

6 months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: MLHFQ total score				
least squares mean (confidence interval 95%)	2.01 (-6.31 to 10.34)	-2.96 (-11.66 to 5.75)		

Statistical analyses

Statistical analysis title	Mixed linear model for repeated measures (MMRM)

Statistical analysis description:

MMRM with change from baseline of MLHFQ total score at month 1, month 3, month 6, month 9, month 12 as dependent variable and treatment, time point and interaction between treatment and time point and baseline MLHFQ as independent variables. Month 6 adjusted mean difference between treatments

was estimated with 95%-confidence interval.

Comparison groups	Placebo v Empagliflozin
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	4.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.09
upper limit	17.03

Primary: EFFORT-2: Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score

End point title	EFFORT-2: Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score

End point description:

Difference of Minnesota Living with Heart Failure Questionnaire (MLHFQ) total score to baseline at 6 months after randomization. A lower MLHFQ score indicates less effect of heart failure on a patient's quality of life. A total score accounts for all 21 items.

End point type	Primary

End point timeframe:

6 months

End point values	Empagliflozin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: MLHFQ total score				
least squares mean (confidence interval 95%)	-5.27 (-11.73 to 1.19)	3.95 (-2.44 to 10.34)		

Statistical analyses

Statistical analysis title	Mixed linear model for repeated measures (MMRM)

Statistical analysis description:

MMRM with change from baseline of MLHFQ total score at month 1, month 3, month 6, month 9, month 12 as dependent variable and treatment, time point and interaction between treatment and time point and baseline MLHFQ as independent variables. Month 6 adjusted mean difference between treatments was estimated with 95%-confidence interval.

Comparison groups	Empagliflozin v Placebo

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	-9.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.35
upper limit	-0.09

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Complete study	
Adverse event reporting additional description:	
Reported adverse events occured in the EFFORT-1 substudy. Adverse events for EFFORT-2 are attached as PDF.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24

Reporting groups	
Reporting group title	Empagliflozin
Reporting group description:	
Empagliflozin	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	Empagliflozin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)	1 / 12 (8.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	2 / 12 (16.67%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			

subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Empagliflozin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)	9 / 12 (75.00%)	

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Finger amputation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Oedema peripheral			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	

Serum ferritin decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Cardiac failure congestive			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Coronary artery disease			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 12 (16.67%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Panophthalmitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Dry mouth			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Gastrointestinal disorder			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	2	
Onychoclasis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Rash			

subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Nocturia			
subjects affected / exposed	2 / 12 (16.67%)	1 / 12 (8.33%)	
occurrences (all)	2	1	
Renal pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Tendon pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Erysipelas			
subjects affected / exposed	0 / 12 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 12 (8.33%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	5 / 12 (41.67%)	
occurrences (all)	0	5	
Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2017	• Visit 2 during the run-in phase has been omitted, as the visit was primarily implemented for controlling of patients' compliance which will be assessed anyway at randomization visit. • Inclusion criterion 1: new: ≤ 85 years old; old: < 85 years old. • Inclusion criterion 3: new: HbA1c ≥ 6.5%; old: HbA1c > 7.0%. • Exclusion criterion 8 has been specified allowing investigators to assess individually a necessary lapse of time preceding registration for patients with implantable cardioverter-defibrillator (ICD) and pacemaker. • Exclusion criterion 16: new: active tumor disease; old: malignancies within the past 5 years (except carcinoma in situ of the cervix and non melanomatous skin cancer). • Definition of MRI compatibility has been included to optimize scheduling the cardiac MRI procedure. • Plasma volume assessment will only be performed in a subgroup of patients due to organizational issues. Patients will be assigned to this examination consecutively beginning from a certain time point in order not to compromise randomisation balance. • In addition to DNA extraction, the biobanking samples will be used for RNA extraction also. • Introduction of time range for randomisation visit. This visit may be postponed for a week due to e.g. bank holidays, patient's medical condition or other patient's related issues. The time range for visit 3 and visit 4 was also extended, up to 7 days. • CTP section related to adverse events of special interest was completed.
17 April 2019	Until April 2019, 54 patients have been randomized within the recruitment period of approximately 29 months since enrolment of the first patient (22 patients in EFFORT-1, 32 patients in EFFORT-2). It was decided to terminate inclusion of patients into the study by the end of 2019, last patient last visit date in January 2021. From a statistical point of view, EFFORT-1, originally planned as a confirmatory study, with a calculated necessary sample size of 200 patients, will now have, with an expected sample size of less than 50 patients, only very low power to detect a difference between treatment arms. So, EFFORT-1, in the same way as planned from the beginning for EFFORT-2, is now regarded as an exploratory hypotheses generating study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The most important limitation is the small number of study participants. As such, the variability of all results is high leading to large confidence intervals of effect estimates.

Notes: